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14. ABSTRACT
African American men have the highest incidence and mortality from prostate cancer in the world. Multiple reasons have been postulated to explain these findings although the definitive reasons for this are unknown. While both environmental and genetic factors may contribute to prostate cancer susceptibility, results from multiple studies consistently implicate a strong genetic component of this cancer. However, a specific gene which is consistently and reproducibly associated with prostate cancer risk in any population has not been identified. Association studies examining the frequency of common but specific genetic variants in study populations with and without a particular disease (i.e. case-control) is a powerful way to detect the influence of common genetic variants capable of affecting disease risk. While these types of studies are powerful, they are not without limitations, including the tendency to be confounded due to population stratification (a critical issue in admixed populations like African American), and the requirement for large, well matched, and well characterized study populations. While there has been extensive use of case control studies to identify genetic risk variants in Caucasian populations, corresponding studies in the African American prostate cancer population have been less extensive, typically being much smaller than the Caucasian counterparts, with little or no efforts to address the critical issue of population stratification as a confounder. It is now quite clear that unless cases are well matched to controls in terms of genetic heterogeneity in such studies, spurious associations will and undoubtedly have been observed and reported. In this study we use Ancestry Informative Markers (AIM) to match African American prostate cancer cases and controls for the purposes of performing association studies without confounding by population stratification. After this matching, we have identified and confirmed several prostate cancer susceptibility loci in this study population, on chromosomes 3, 8 and 17. These and other ongoing studies will provide important insight into the role of inherited factors in prostate carcinogenesis in African Americans.

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INTRODUCTION

African American men have the highest incidence and mortality from prostate cancer in the world. Multiple reasons have been postulated to explain these findings including access to care, attitudes about care, socioeconomic and education differences, differences in type and aggressiveness of treatment, dietary, and genetic differences, although the definitive reasons for this are unknown. Indeed, the reasons why any prostate cancers occur are incompletely understood, and the only consistent risk factors identified for prostate cancer in addition to race are age and family history. While both environmental and genetic factors may contribute to prostate cancer susceptibility, results from multiple studies consistently implicate a strong genetic component of this cancer, with an estimated heritability of 42%, the highest among all common cancers. However, despite years of extensive effort by multiple research groups world wide, a specific gene which is consistently and reproducibly associated with prostate cancer risk in any population has not been identified. Association studies examining the frequency of common but specific genetic variants in study populations with and without a particular disease (i.e. case-control) is a powerful way to detect the influence of common genetic variants capable of affecting disease risk. While these types of studies are powerful, they are not without limitations, including the tendency to be confounded due to population stratification (a critical issue in admixed populations like African American), and the requirement for large, well matched, and well characterized study populations. While there has been extensive use of case control studies to identify genetic risk variants in Caucasian populations, corresponding studies in the African American prostate cancer population have been less extensive, typically being much smaller than the Caucasian counterparts, with little or no efforts to address the critical issue of population stratification as a confounder. It is now quite clear that unless cases are well matched to controls in terms of genetic heterogeneity in such studies, spurious associations will and undoubtedly have been observed and reported. In this study we use Ancestry Informative Markers (AIMs) to match African American prostate cancer cases and controls for the purposes of performing association studies without confounding by population stratification. We have identified and confirmed several prostate cancer susceptibility loci in these studies, on chromosomes 3, 8 and 17. These and other ongoing studies will provide unprecedented insight into the role of inherited factors in prostate carcinogenesis in African Americans.

BODY: To date, we have genotyped 58 AIMs in our study population. Genotyping this matched case control population for SNPs led to the discovery of an additional prostate cancer susceptibility locus at 8q24 (rs16901979) (Gudmundsson et al 2007). The risk allele ("A") at this locus is present in 50% of our African American cases, compared to 42% of controls. Importantly, this locus also shows association with risk for prostate cancer in European Americans although the risk allele is much less common in this population (~3% in controls, ~6% in cases); the OR of ~1.8 for this latter population is the largest effect observed to date for any SNP. These data indicate that the same locus can affect risk of prostate cancer in multiple different ancestral populations, although the effects and risk allele frequencies may be very different. More recently, we completed genotyping of an additional 7 SNPs on chromosome 17 in our matched African American case control population (Sun et al 2008). These analyses provided the first evidence that SNPs at 17q12 are associated with risk of prostate cancer in African Americans. In this case the risk allele (T at rs4430796) is less common in African Americans than it is in European Americans.

To address the general question of whether or not prostate cancer risk alleles identified in European Americans are also associated with risk in African Americans, we evaluated 20 known risk SNPs in 868 African American prostate cancer cases and 878 controls (Xu et al 2009). For 17 of these 20 SNPs, implicated risk-associated alleles were found to be more common in these AA cases than controls, significantly more than expected under the null hypothesis ($P = 0.03$). A multivariate analysis of additional SNPs across the broader 8q24 region revealed three independent prostate cancer risk-associated SNPs, including rs16901979, rs13254738, and rs10086908. The first two SNPs were approximately 20 kb apart and the last SNP, a novel finding from this study, was approximately 100 kb centromeric to the first two SNPs. These results suggest that a systematic evaluation of regions harboring known prostate cancer risk SNPs implicated in other races is an efficient approach to identify risk alleles for AA. However,

studies with larger numbers of AA subjects are needed, and this has required a major collaborative effort to combine multiple AA study populations. Such a study has now been performed and reported by Haiman et al (2011). This study included our AA subjects in a combined analysis of 3425 AA prostate cancer cases and 3290 AA controls. This study validated and improved upon markers of risk in some regions that better define the association with prostate cancer in African Americans. The findings with variants at 8q24 reinforce the importance of this region as a major risk locus for prostate cancer in men of African ancestry.

It has become clear that many men are diagnosed with and treated for prostate cancer that is destined never to progress. While the extent of this over-diagnosis problem is less clear in the African American population, it is evident that the identification of SNPs with prognostic significance would be of value for essentially all male populations. To address this issue we are continuing our search for risk SNPs which have prognostic significance in African American men.

KEY RESEARCH ACCOMPLISHMENTS:

- Our African American case control population has been genotyped for a panel of AIMs
- Matching of cases and controls based on average percent African American ancestry has been accomplished
- Genotyping of 8q24 markers in this population led to the discovery of a novel prostate cancer risk variant (rs16091970) that is reproducibly associated with prostate cancer in African American men
- Genotyping of 17q12 markers in this population provided the first demonstration that rs4430796 is associated with prostate cancer risk in African American men.
- Genotyping of 20 SNPs markers in this population provided the first systematic analysis in African Americans of SNPs shown to be associated with prostate cancer risk in men of European descent.
- Our African American case control population was part of a large analysis fine mapping and refining the role of SNPs in prostate cancer risk in this population
- A summary of the progress on this project was presented at the IMPACT meeting in Florida in Spring 2011.

REPORTABLE OUTCOMES

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CONCLUSIONS

Ancestry mapping of African American prostate cancer cases and controls allows for the identification and characterization of genetic risk factors that are significantly and reproducibly associated with prostate cancer risk in this high risk population.